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Full Length Article

Effect of *Gymnema lactiferum* tea brew on type 2 diabetes mellitus: A double-blind, randomised active-controlled phase III clinical trial

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ABSTRACT

Background: *Gymnema lactiferum* is an edible leafy vegetable plant in the family of Apocynaceae. It has been used to control diabetes in the northern part of Sri Lanka for several decades and used as a leaf vegetable from the ancient period. However, this plant was not clinically tested for its claimed antidiabetic properties. Therefore, this study was conducted in Teaching Hospital Jaffna to establish the efficacy of the plant.
Objective: The objective of this parallel arm, double-blind randomised controlled phase III trial is to establish the efficacy and safety of *Gymnema lactiferum.*
Methods: Eligible type 2 diabetes mellitus (T2DM) patients at the Diabetic Centre, Teaching Hospital Jaffna, Sri Lanka were randomly allocated to treatment (n = 160) and control (n = 160) arms. The treatment arm received a tea brew made of *G. lactiferum* dried leaves (1.5 g in 200 mL of hot water) while the control arm received green tea (1.5 g in 200 mL of hot water) daily for 3 months. The patients in both arms were reviewed at the baseline and the end of 1st, 3rd and 6th months for FPG, HbA1c, blood pressure, body weight and lipid profiles.
Results: Statistically significant reductions in HbA1c (treatment arm: -0.47 %, P = 0.0000; control arm -0.26 %, P = 0.0009) and FPG (the control arm: −0.42 mmol/L, P = 0.0388) from the base values were observed at the end of the 3rd month. In the subgroup analysis that evaluated the participants with poorly controlled glycemia (HbA1c ≥8), which accounted for over 52 % of all participants, a clinically significant reduction in HbA1c was observed in the treatment and control arms (-0.90 %; P = 0.0000 and -0.71 %; P = 0.0000). Post-intervention analysis revealed a long-lasting significant reduction in HbA1c in both arms. Further, significant reductions in blood pressure and lipid profile were also noted at the end of the third month and post-intervention period.
Conclusion: *G. lactiferum* tea significantly reduced HbA1c in uncontrolled T2DM patients and the effect observed was superior to green tea. Long-term treatment is needed to determine the clinical implications of the effects on blood pressure, body weight and lipid levels and to confirm the safety.

1. Introduction

Diabetes mellitus is one of the major non-communicable diseases affecting more than 422 million people worldwide, and its prevalence is increasing rapidly in low- and middle-income countries (WHO.,2016). Complementary and alternative medicines (CAM) by patients with diabetes is increasing worldwide (Birdee et al., 2010, Vishnu et al., 2017, Radwan et al., 2020, Kifle et al., 2021, Shahjalal et al., 2022). The major concern regarding the use of CAM is the lack of evidence for the efficacy and safety of these medicines (Birdee et al., 2010, Kifle et al., 2021). A study conducted among patients with type 2 diabetes mellitus (T2DM) in Sri Lanka reported that 76 % of them use CAM, including herbal products, to reduce their blood glucose (Medagama at el., 2014). *Gymnema lactiferum (G. lactiferum)* is a commonly used CAM in Sri Lanka (Tamil name Cherukurinja; Singhala name: Kuringnan) (Wasana et al., 2021). *G. lactiferum* leaves have been chewed as raw in northern Sri Lanka mainly by Diabetic patients from ancient times.

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Fig. 1. Pictures of ***Gymnema lactiferum*** and the chemical structure of Gymnemic acid.
R1- tigloyl / 2-methyl butanol, R2- acetyl / H, e.g.- Gymnimic acid I- R1-tigloyl and R2-acetyl, Gymnemic acid II- R1- 2-methyl butanol and R2- acetyl, Gymnemic acid III- R1- 2-methyl butanol and R2- H.

G. lactiferum and the other well-known species, *G. sylvestre*, are woody climbers belonging to the Apocynaceae family (sub-family of Asclapiadaceae) distributed throughout India, Malaysia and Sri Lanka. Leaves of both climbers have the property of controlling the blood sugar and lipids in diabetic patients (Baskaran et al., 1990, Kanetkar et al., 2007, Thushari et al., 2010, Kang et al., 2012, Wasana et al., 2021). *G. lactiferum* is used as a food supplement to control diabetes in alternative medicine and has been used as a leafy vegetable in Sri Lanka from ancient times mainly by diabetes mellitus patients. The leaves are used to make an Ayurvedic drug, "Mathumehachooranam", to treat diabetic patients in Ayurvedic Hospitals in Sri Lanka. The active component of the "Mathumehachooranam" is *G. lactiferum* leaves. Gymnemic acids (Fig. 1) are the bioactive components reported to be found in the Gymnema leaves. The hypoglycaemic effects of Gymnemic acids are reported to be due to the facilitation of secretion of insulin, promotion of regeneration of islet cells, increased utilisation of glucose by increasing the activities of enzymes responsible for the utilisation of glucose in insulin-dependent pathways, increased phosphorylase activity, decreasing gluconeogenic enzymes and sorbitol dehydrogenase activities and act as a competitive inhibiter of glucose absorption from the intestine (Sahu et al., 1996, Persaud et al., 1999, Kanetkar et al., 2004, Kanetkar et al., 2007, Tiwari et al., 2014, Khan et al., 2019). Several Gymnemic acid derivatives such as Gymnemic acids I, II, and III have been reported to be obtained from the hot water extract of Gymnema leaves (Rastogi et al., 1990, Kadiragamanathar et al., 2009, Tiwari et al., 2014).

G. lactiferum trees grow freely in the dry forests and home gardens of Sri Lanka and are cultivated in diabetic patients' home gardens in the northern part of Sri Lanka for their use. The leaves are usually chewed raw by diabetic patients to control blood glucose. Further, a herbal tea produced from *G. lactiferum* leaf is registered by a company under the brand name Gym Diabetic Tea under the Department of Ayurveda, Sri Lanka (Reg. No – 02/01/AF/14/687) and available over the counter in the market for Diabetes Mellitus patients.

So far only one study on *G. lactiferum* in human subjects is available but with sample size and methodological inadequacies (Thushari et al., 2009). The present study was conducted in the Teaching Hospital, Jaffna, Sri Lanka by preparing a *G. lactiferum* herbal Tea. This parallel arm double-blind randomised controlled phase III trial was conducted in TH Jaffna to establish the efficacy and safety of *G. lactiferum* leaf because of a fairly large population of diabetic patients using the *G.lactiferum* leaf on and off in addition to their conventional drugs to control the blood sugar without proper scientific studies or proper medical advice.

2. Methods

2.1. Clinical trial

This clinical study was conducted as a double-blind, active controlled, phase III clinical trial from October 2019 to August 2022 in the Diabetic Centre, Teaching Hospital Jaffna under Good Clinical Practice (GCP) and Declaration of Helsinki guidelines. Ethical clearance was obtained from the Ethics Review Committee, Faculty of Medicine, University of Jaffna (Reg. No- J/ERC/15/66/NDR/013, date: - 11.01.2016). The study was registered under the Sri Lanka Clinical Trial Registry (Reg. No - SLRT/2016/007, date: - 09.03.2016) and the WHO Clinical Trial platform (Universal registration number U1111-1177- 0604).

2.2. Objective

The specific objective of the research was to determine the supplement effects of *G. lactiferum* on glycaemic control in T2DM diabetic patients and the effect on selected biochemical and physiological parameters such as body weight, blood pressure, lipid profile, liver function, renal function and full blood count.

2.3. Test materials

The test product was a tea brew made out of *G. lactiferum* dried leaf, and the active control was Green tea (*Camellia sinensis*). *G. lactiferum* leaves were obtained from a single farm in northern Sri Lanka to minimize variations. They were authenticated by an experienced traditional medical practitioner of the herbal company, Bio Tec International, Jaffna, Sri Lanka and assisted in preparing powdered dried leaves of *G. lactiferum* for the study. The commercially available herbal tea of *G. lactiferum*, the Gym Diabetic Tea contains 1.5 g of powdered dried leaves of *G. lactiferum* in each bag. Daily intake was mentioned in the registered product as one cup of tea at a time, made from one tea bag, and three times a day max. Chemical analysis or purity testing of *G. lactiferum* dry leaves was performed before the clinical trial at accredited testing laboratories at Industrial Technology Institute, Colombo, Sri Lanka to ensure microbial purity and free of heavy metals and pesticide residues. Green tea was obtained from a single manufacturer (Melfort Green Teas - Pvt Ltd, Pussellawa, Sri Lanka.).

Each test and control tea bag contained 1.5 g of *G. lactiferum* and green tea, respectively. All tea bags were prepared and packed before the recruitment of participants. The external appearance and labelling of both tea bags were the kept same. To blind the investigators and the participants, participants' numbers, according to the group, were written on the tea bags, by the packing company. Neither the investigators nor the participants revealed the identity of the treatment and control products until after the statistical analysis of the data was completed.

2.4. Quantification of Gymnemic acids in G. lactiferum tea brew

The moisture content in *G. lactiferum* tea powder was measured according to ISO 287:2017 for moisture determination. Gymnemic acids present in the *G. lactiferum* tea extract were first converted to gymnemagenin and the total gymnemagenin content was then estimated using a standard solution of gymnemagenin using High-Performance Liquid Chromatography (HPLC) (Agilent Technologies 1260 Infinity II) with

Table 1
Summarised study schedule.

Parameters	Period of review			
	Baseline visit	End of 1st month	End of 3rd month	End of 6th month (Post-intervention visit)
History and examination	√	√	√	√
Blood pressure	√	√	√	√
Body weight	√	√	√	√
FPG	√	√	√	√
HbA1c	√	-	√	√
Lipid profile	√	-	√	√
FBC	√	√	√	√
Serum creatinine	√	√	√	√
ALT	√	√	√	√
AST	√	√	√	√

√= analysed, - = not analysed

variable wavelength detector (1260 DAD WR) operating at 210 nm. Separations were carried out with SUPELCOSIL^{TM} LC-18 (25 cm × 4.6 mm, 5 μm) column with a column temperature of 30 °C. The mobile phase was acetonitrile water (50:50) with a 1 mL/min elution rate. The HPLC analysis was carried out in duplicate. Calculation of gymnemic acids component from the total gymnemagenin quantified by HPL was done using the equation: C= X (809.0/ 506.7) where C is the content of gymnemic acid in the sample; X is the content of gymnemagenin present in the sample; 506.7 is the molecular weight of gymnemagenin, and 809.0 is the molecular weight of gymnemic acid. The conversion of gymnemic acid into gymnemagenin for the HPLC analysis was carried out as described by Verme et al 2016. Briefly, *G. lactiferum* tea (1.5 g) in 50 mL of water with 10 mL of 11 % potassium hydroxide was refluxed for an hour and refluxed again for one hour after adding 9 mL of concentrated HCl. The mixture was then cooled down to room temperature, filtered and made up to 100 mL with water. The solution was filtered through a 0.45 μm nylon filter (Millipore) and used for HPLC analysis (Verma et al., 2016).

2.5. Study design

A total of 778 T2DM patients on oral hypoglycemic drugs were screened and 320 were recruited between October 2019 and February 2022 in the diabetic centre, Teaching Hospital Jaffna. Pregnant or lactating women, patients with end-stage organ failure or difficulty in communication, patients who were taking insulin or medications that may raise blood glucose and those who were already taking *G. lactiferum* supplement and or green tea were excluded. The numbers for the selected participants were allocated by the research assistants according to the arrival time during the recruitment process. They were assigned to the groups by the PI by their participant number. Code numbers from 1 to 320 were created and randomly assigned to each group using computer-generated randomization by another person who was not on the research team. The recruited patients were randomly allocated into the treatment and control groups. The sample size for each arm was determined with 80 % power at a 5 % significance level (Sakpal et al., 2010) using the changes in mean HbA1c reported by a study that compared a Sitagliptin/metformin fixed-dose combination (Reasner et al., 2011). Assuming 10 % dropouts, the estimated sample size was 160 per group. Informed consent was obtained from each participant on recruitment.

2.6. Data collection and safety outcomes

At the time of recruitment, information about sociodemographic characteristics, disease profile and medications was obtained and a physical examination was performed and recorded. Blood pressure and body weight were measured and blood samples were taken to determine the baseline values. Participants were reviewed at the end of one month, three months of treatment, and six months of post-treatment. Blood parameters, blood pressure and body weight measurements were repeated at the end of 1, 3 and 6 months except for HbA1c level and lipid profile. HbA1c levels and lipid profiles were repeated at the end of 3 and 6 months (Table 1).

The collected blood samples were sent to the clinical laboratory at the Teaching Hospital Jaffna immediately after the collection. At each visit, the participants were reviewed for adverse effects, any changes in the treatment and the count of the remaining tea bags to estimate the compliance of patients.

Height, body weight and blood pressure were taken according to the WHO standard. Body weight was measured using an electronic digital weighing scale in kg with two decimal accuracy. Height was measured in meters with a two-decimal accuracy. The blood pressure was measured in the seated position after a resting period of 5 minutes using an electronic blood pressure recorder. An average of two readings in mmHg was recorded.

A third reading was taken if both readings showed a variation of over 20 mm Hg. The average of any of the two readings which shows a narrow variation was considered for the analysis. All the above measurements were taken using standard clinical equipment. *G. lactiferum* tea bags and green tea bags were given to the participants according to the number written on each tea bag, at the baseline visit. Participants were asked to consume one cup (200 mL) tea or green tea once a day for 90 days and not to take them after 90 days up to the 6-month visit. They were instructed to prepare the tea by placing a tea bag in a cup containing 200 mL of hot water and stirring for 5 minutes. The participants were told to continue their regular medications, usual diets and activity during the intervention period. Participants were also asked to report any adverse effects at any time through a hotline telephone number and next visit dates were given. No alterations were made after the commencement of the trial. Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of the research.

All biochemical tests were performed by Siemens dimension EXL 200 fully automated clinical chemistry analyser (USA) with dedicated reagents at the Chemical Pathology laboratory in the Teaching Hospital, Jaffna. Plasma glucose assay was performed by enzymatic colorimetric method (Hexokinase, glucose-6-phosphate dehydrogenase method), HbA1c by turbidimetric inhibition immunoassay (TINIA); total cholesterol by enzymatic colorimetric method (cholesterol esterase, cholesterol oxidase, Peroxidase method); triglyceride by enzymatic colorimetric method (lipoprotein lipase, glycerol kinase, glycerol-3-phosphate oxidase, peroxidase); HDL cholesterol by the direct method and LDL cholesterol by the homogenous direct method; AST by enzymatic colorimetric method (Aspartate, α ketoglutarate, oxalacetate coupled reaction) and ALT by enzymatic colorimetric method (Alanine, α ketoglutarate, pyruvate coupled reaction) and Serum creatinine by modified Jaffe kinetic method (IDMS traceable).

FBC was done by a fully automated 7-part Haematology analyser (Sysmex XN 1000), Hb was done by calorimetry method, WBC (White

blood cell) was done by flow cell counting, and the Differential count was done by dye-binding method

2.7. Data analysis

Data from participants who completed the 6-month follow-up without interruption were analysed. Descriptive statistics such as frequency, percentage, mean ± standard deviation (SD) and change in means were used to present the data. Independent t-tests and paired t-tests were used to determine the difference in continuous variables between and within the groups respectively, using SPSS software (Version 26) and Excel Sheet. Independent t-tests with 95 % confidence intervals (CIs) were used to compare the categorical variables of the test and control groups. All the tests were two-tailed, and a *P*-value <0.05 was considered statistically significant.

Primary endpoints were changes in HbA1c from baseline to the end of the 3rd and 6th months (post-intervention) and changes in FPG from baseline to the end of the 1st, 3rd and 6th months.

Secondary endpoints were changes in blood pressure, body weight and lipid profile from the bass line to 3 and 6 months.

Subgroup analyses of changes in HbA1c among subsets of participants with HbA1c levels <7 %, ≥7 % to <8 % and ≥8 % and changes in BP among the participants with and without hypertension were carried out.

3. Results

3.1. Gymnemic acids content

Quantitative estimation revealed a 1.5g tea bag contains 15.60 ± 0.34 mg of active biomarker gymnemic acids.

3.2. Sample characteristics

Out of the 160 patients per arm, 146 (91.3 %) in the treatment arm and 142 (88.6 %) in the control arm completed the study without interruption (Fig. 2). The mean ages of the test and control arms were 58.7 ± 10.5 years and 56.7 ± 11.1 years, respectively. The majority were females in the treatment arm (60.2 %), whereas the number of males and females was almost equal in the control arm. All the participants were Sri Lankan Tamils except one Sri Lankan Sinhalese. Most of the participants had T2DM for more than 5 years (61.0 %) in the treatment arm and 62 % in the control arm. The majority of the participants received metformin and Gliclazide (test- 44.4 %; control- 47.5 %), Metformin was the most frequently used medication, prescribed to more than 90 % of the participants in both arms (Table 2).

3.3. Clinical and biochemical effects of Gymnema lactiferum treatment

The mean HbA1c and FPG (Fasting Plasma Glucose) in the treatment and control arms were 8.31 ± 1.79 %, 8.07 ± 1.38 % and 7.99 ± 2.41 mmol /L, 8.25 ± 2.70mmol/L respectively (Table 3). There is a significant reduction in the HbA1c in three months was noted in the treatment arm (-0.47 %; *P*<0.0000) and control arm (-0.26 %; *P*<0.0009). The post-intervention review showed a significant increase in mean HbA1c from the 3rd month in the treatment arm (test=0.22 % with *P* = 0.0040) whereas it was not significant in the control arm (control=0.16 % with *P* = 0.0908). The subgroup analysis showed that the reduction in mean HbA1c occurred only in the subgroup of participants with baseline HbA1c ≥8 % in the treatment and control arms, and the reductions were -0.90 % (*P* = 0.0000) and -0.71 % (*P* = 0.0000), respectively (Fig. 3). In the HbA1c ≥ 8 subgroups, the reduction from baseline in HbA1c remained at -0.75 % (*P* = 0.000) in the treatment arm and -0.73 % (*P* = 0.000) in the control arm in the post-intervention period. These post-intervention readings show that the reduction in HbA1c was long-lasting beyond 3 months in poorly controlled diabetes participants.

There was no significant reduction in FPG at the end of 1st and 3rd month in the treatment arm (Table 3). In the control arm, a significant reduction was noted in the 3rd month (-0.42 mmol/L; *P* = 0.0388) (Fig. 4).

In the subgroup of HbA1c≥8, a significant reduction was noted in the FPG in the control arm during the 3rd month period (-0.75 mmol/L: *P* = 0.0284) and in the treatment arm during the post-intervention period (-0.87 mmol/L; *P* = 0.0134).

A significant reduction in mean SBP (Systolic blood pressure) at the end of 3 months in the treatment and control arms was observed [-2.77 mmHg (*P* = 0.0375) and -2.66 mmHg (*P* = 0.0390) respectively] (Fig. 5). The post-intervention review after 6 months showed a greater reduction in mean systolic blood pressure in the treatment arm [-3.6 mmHg (*P* = 0.0072)] whereas; in the control arm, it was statistically insignificant [-0.99 mmHg (*P* = 0.4797)] (Fig. 5).

The reduction in mean DBP (Diastolic blood pressure) at the end of 3 months in the test and control arms was -3.2 mmHg (*P* = 0.0000) and -2.3 mmHg (*P* = 0.0030). The post-intervention review of diastolic blood pressure showed a greater reduction in the treatment arm [-4.5 mmHg (*P* = 0.0000)] and in the control arm, it was -1.9 mmHg (*P* = 0.0343).

Subgroup analysis among participants with HT showed progressive reductions in both systolic and diastolic blood pressure in the treatment and control arms (Table 3).

Reduction in mean systolic blood pressure at the end of 3 months in the treatment and control arms in hypertension patients were -10.46 mmHg (*P* = 0.0000) and -8.22 mmHg (*P* = 0.0000) respectively. The reduction of mean systolic blood pressure of the post-intervention period in the treatment and control arms were -12.82 mmHg(*P* = 0.0000) and -9.085 mmHg (*P* = 0.0000) respectively.

Subgroup analysis among participants without HT showed any significant reduction in any of the arms.

The reduction in the mean BW (Body weight) in the treatment arm at 3 months was -0.27 kg; (*P* = 0.0343) and in the post-intervention period it was -0.52 kg; (*P* = 0.0012) (Table 3) In the control arm the reduction in the body weight was not significant in 3 months (-0.20 kg; *P* = 0.2106) whereas a significant reduction was observed in the postintervention period (0.45 kg; *P* = 0.0355).

In the total cholesterol, A significant reduction (*P*<0.05) in 3 months was observed in the treatment arm (-0.22 mmol/L; *P* = 0.0008) and in the control arm the reduction was -0.18 mmol/L; *P* = 0.0095. In the post-intervention period the reduction treatment arm remained at -0.20 mmol/L; *P* = 0.0083 and in the control arm it was not significant (-0.08 mmol/L; *P* = 0.2805) (Fig. 6).

A significant reduction was observed in the triglycerides in 3 months in the treatment arm (-0.14 mmol/L; *P* = 0.0003) and in the control arm, it was -0.13 mmol/L; *P* = 0.0003. In the post-intervention period in the treatment arm, it was -0.08mmol/L; *P* = 0.0559 and in the control arm, it was – 0.08 mmol/L; *P* = 0.0243.

In the treatment arm, the LDL cholesterol (Low-density lipoprotein) was significantly reduced in the treatment arm (-0.16mmol/L; *P* = 0.0053) and in the control arm, it was not significant(0.06 mmol/L; *P* = 0.2850). In the post-intervention period the reduction in LDL in the treatment arm was -0.26mmol/L; *P* = 0.0000 and in the control arm, it was -0.13mmol/L; *P* = 0.0333.

HDL cholesterol(High-density lipoprotein) was not significantly reduced in the treatment arm in 3 months (-0.01mmol/L; *P* = 0.7398) and in the control arm, it was significantly reduced (-0.03mmol/L; *P* = 0.0283). In the post-intervention period, the reduction in HDL in the treatment arm and control arm was not significant (0.03 mmol/L; *P* = 0.0566 and -0.03 mmol/L; *P* = 0.2739) (Fig. 6).

3.4. Adverse effects, dropouts and compliance

Both treatment and control products were well tolerated. Less than 5 % reported dizziness, palpitation and tiredness (Table 4). No hypoglycaemic episodes or serious adverse events were reported in either arm.

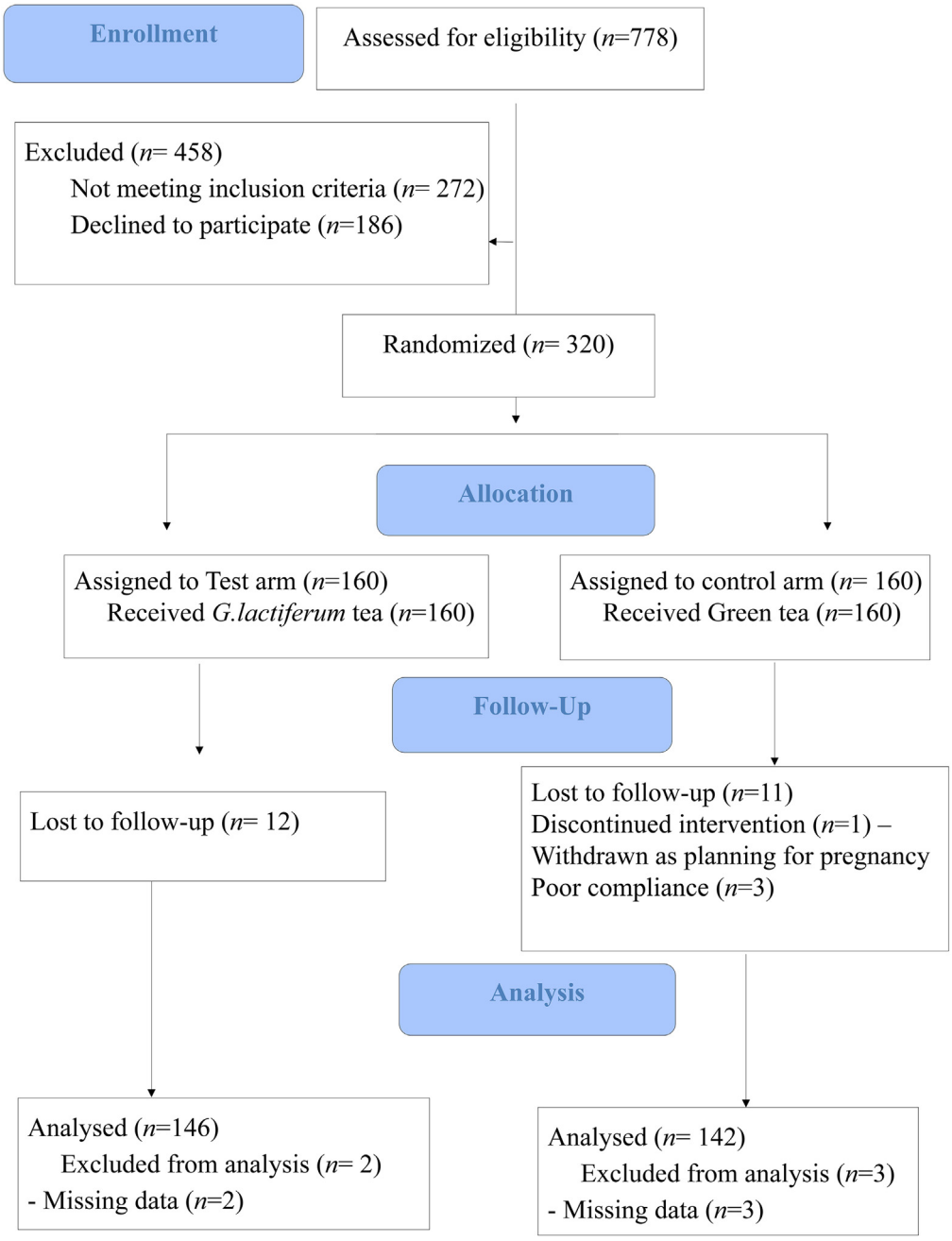

Fig. 2. CONSORT flow diagram.

The mean WBC, Platelet, Hb (Haemoglobin), ALT (Alanine aminotransferase), AST (Aspartate aminotransferase) and Creatinine were within normal levels at the baseline, in 3rd month and the post-intervention period. However, both arms showed a reduction in eGFR (Estimated Glomerular filtration rate), ALT, AST and haemoglobin (Table 3). The reduction in eGFR in the treatment arm was -6.68 mL/min/1.73 m^2 (P = 0.00001) and -5.88 mL/min/1.73 m^2 (P = 0.0000) in the control arm . Haemoglobin was reduced by 0.23 % (P = 0.0011) in the treatment arm and by 0.27 % (P = 0.0010) in the control arm compared to respective baseline values. The reduction in the ALT in the treatment arm was – 6.10 U/L (P = 0.0000) and in the control arm was -3.78 U/L (P = 0.0009). The reduction in the AST in the treatment arm was -5.23 U/L (P = 0.0000) and in the control arm, it was -1.34 U/L (P = 0.0749).

The post-intervention review showed a reduction in eGFR and haemoglobin in both arms. The treatment arm showed a -12.00 mL/min/1.73 m^2 (P = 0.0000), and the control arm showed an -11.03 mL/min/1.73 m^2 (P = 0.0000) reduction in eGFR. The reductions in haemoglobin in the treatment and control arms were -0.59 % (P<0.0000) and -0.47 % (P = 0.0000), respectively.

The reduction in the ALT in the treatment arm was -6.38 U/L (P = 0.0000) and the control arm was -4.67 U/L (P = 0.0012). The reduction in the AST was -4.05 U/L (P = 0.0010) and the control arm was -0.023 U/L (P = 0.9806).

4. Discussion

The use of CAM among patients with T2DM in Sri Lanka is high (Medagama at el., 2014) despite the lack of evidence on its efficacy and safety. This paper discusses the effects of *G. lactiferum* in participants with T2DM, which is one of the commonly used herbal medicines in Sri Lanka, particularly in the northern region. Without a proper scientific study, patients are taking the leaves to control their blood sugar.

Table 2
Baseline characteristics of the participants.

Variables	Test (n = 146)	Control (n = 142)
Age (years)	58·7 ± 10.5	56·8 ± 11.1
Sex		
Male	58 (39.7 %)	75 (46.9 %)
Female	88 (60.2 %)	85 (53.1 %)
Duration of diabetes mellitus (years)		
< 5 years	57 (39.0 %)	54 (38.0 %)
5 to 10 years	47 (32.2 %)	55 (38.7 %)
>10 years	42 (28.8 %)	35 (23.2 %)
Treatment		
Metformin	59 (36.9 %)	54 (33.8 %)
Gliclazide	10 (6.3 %)	5 (3.1 %)
Metformin + Gliclazide	71 (44.4 %)	77 (47.5 %)
Metformin + Sitagliptin	3 (1.9 %)	0
Metformin + Tolbutamide	3 (1.9 %)	4 (2.5 %)
Metformin + Glibenclamide	0	1 (0.6 %)
Gliclazide + Sitagliptin	0	1 (0.6 %)
Metformin + Gliclazide + Sitagliptin	12 (7.5 %)	19 (11.9 %)
Metformin +Gliclazide+ Pioglitazone	1 (0.6 %)	0
Metformin + Gliclazide+ Sitagliptin + Glimepiride	1 (0.6 %)	0
HbA1c (%)	8.46 ± 1.92	8.35 ± 1.70
HbA1c subgroups		
Baseline HbA1c <7 %	33 (22.6 %)	29 (20.4 %)
Baseline HbA1c ≥7 % to <8 %	37 (25.3 %)	37 (26.1 %)
Baseline HbA1c ≥8 %	76 (52.1 %)	76 (53.5 %)
FPG (mmol /L)	8.5 ± 3.1	8.5 ± 3.0
Bodyweight (kg)	64.3 ± 12.1	65.9 ± 13.1
Systolic blood pressure (mmHg)	130.6 ± 21.4	131.4 ± 20.2
Diastolic blood pressure (mmHg)	81.8 ± 12.1	81.3 ± 11.1
Lipid profile		
Total cholesterol (mmol /L)	4.3 ± 1.0	4.2 ± 1.0
LDL cholesterol (mmol /L)	2.4 ± 0.8	2.3 ± 0.9
Triglycerides (mmol /L)	1.4 ± 0.7	1.3 ± 0.6
HDL cholesterol (mmol /L)	1.4 ± 0.5	1.3 ± 0.5

Data are presented as Mean ± SD or percentage. FPG = fasting plasma glucose, LDL= low-density lipoprotein, HDL= high-density lipoprotein.

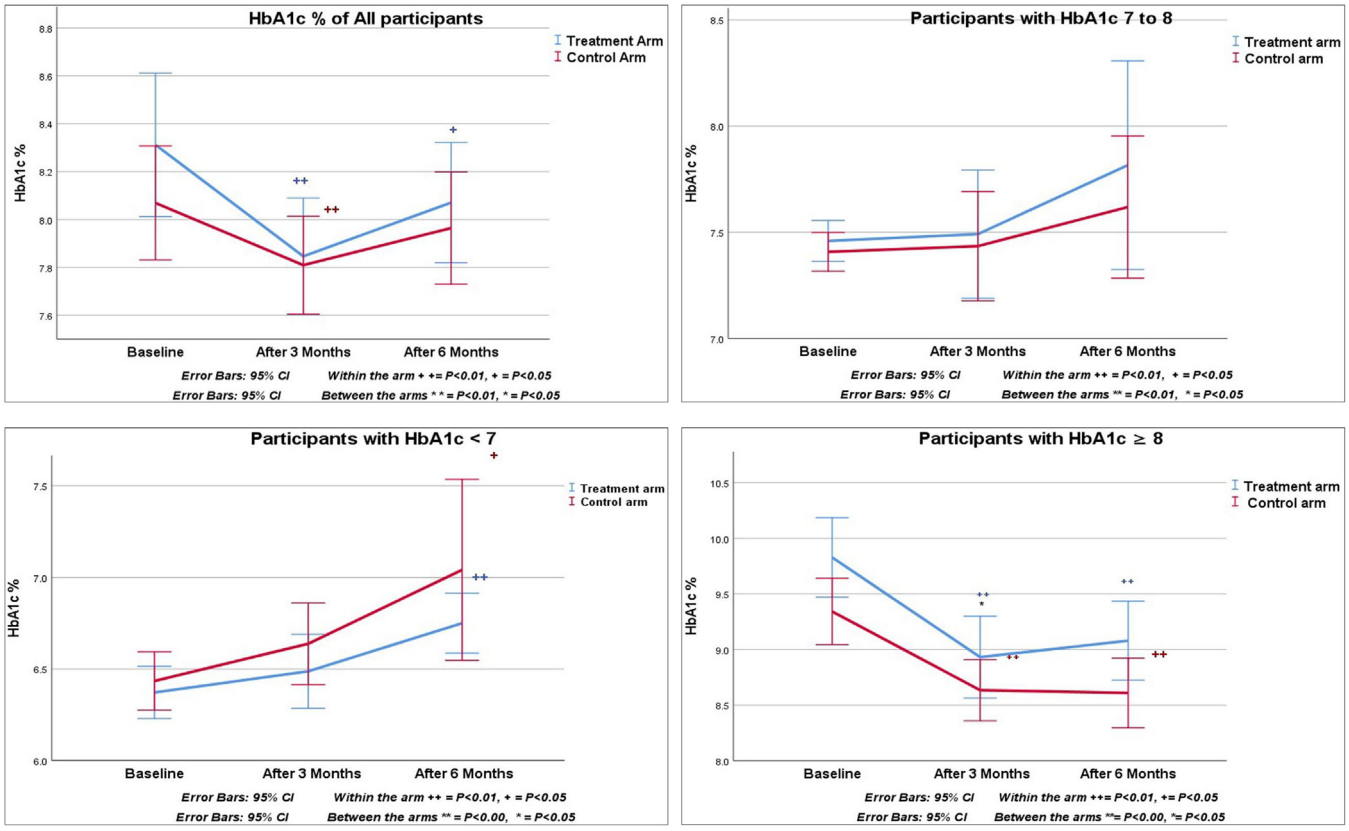

Fig. 3. Changes in HbA1c in test and control arms.

Table 3
Clinical and biochemical data of T2DM patients in the *Gymnema lactiferum* or Green Tea administered groups.

Findings	Control Group (Green Tea-*n* = 142)				Treatment Group (Gymnema lactiferum- *n* = 146)			
	Baseline (Mean ± SD)	1st Month (Mean ± SD)	3rd Month (Mean ± SD)	6th Month (Mean ± SD)	Baseline (Mean ± SD)	1st Month (Mean ± SD)	3rd Month (Mean ± SD)	6th Month (Mean ± SD)
FPG (mmol/L)	8.25 ± 2.70	8.48 ± 2.57	7.82 ± 2.19	8.04 ± 2.43	7.99 ± 2.41	7.84 ± 2.29*	7.80 ± 2.40	7.76 ± 2.43
FPG (in HbA1c <7)	5.90 ± 0.90	6.18 ± 0.90	6.19 ± 0.95	6.62 ± 1.45	6.11 ± 0.81	5.98 ± 0.66	5.95 ± 0.86	6.39 ± 0.80
FPG (in HbA1c ≥7 to <8)	6.77 ± 1.42	7.21 ± 1.38	7.11 ± 1.21	7.07 ± 1.59	6.87 ± 1.11	7.15 ± 1.59	7.32 ± 1.59	7.30 ± 1.64
FPG (in HbA1c ≥ 8)	9.87 ± 2.67	10.00 ± 2.50	9.11 ± 2.90	9.27 ± 2.97	9.70 ± 2.63	9.63 ± 2.99	9.19 ± 2.86	8.83 ± 2.70
HbA1c (%)	8.07 ± 1.38	-	7.81 ± 1.18	7.96 ± 1.36	8.31 ± 1.79	-	7.85 ± 1.45	8.07 ± 1.50
HbA1c (< 7)	6.43 ± 0.42	-	6.64 ± 0.59	7.04 ± 1.30	6.37 ± 0.40	-	6.75 ± 0.45	6.70 ± 0.37
HbA1c (≥7 to <8)	7.41 ± 0.27	-	7.44 ± 0.77	7.62 ± 1.00	7.46 ± 0.29	-	7.49 ± 0.91	7.82 ± 1.47
HbA1c(≥8)	9.34 ± 1.24	-	8.64 ± 1.14	8.61 ± 1.30	9.83 ± 1.55*	-	8.93 ± 1.60	9.08 ± 1.54
BW (kg)	64.14 ± 10.37	64.18 ± 10.25	63.93 ± 10.46	63.68 ± 10.46	63.49 ± 11.05	63.50 ± 11.03	63.23 ± 11.06	62.98 ± 11.04
SBP (mmHg)	130.09 ± 18.69	128.39 ± 16.19	127.43 ± 14.93	129.10 ± 15.62	127.69 ± 17.48	126.74 ± 15.93	124.91 ± 16.68	124.11 ± 15.35*
SBP (in Patients with HT)	145.69 ± 11.14	136.31 ± 15.14	137.47 ± 13.84	135.86 ± 14.60	145.23 ± 12.19	135.30 ± 15.53	134.77 ± 17.35	132.39 ± 13.34
SBP (in Patients without HT)	116.55 ± 8.71	120.64 ± 11.84	118.45 ± 10.92	121.85 ± 11.55	116.38 ± 9.72	120.62 ± 13.36	118.12 ± 13.03	117.12 ± 10.87*
DBP(mmHg)	80.36 ± 10.00	79.16 ± 9.21	78.07 ± 8.39	78.42 ± 9.47	79.90 ± 9.947	78.30 ± 9.24	76.66 ± 8.54	75.37 ± 8.15*
DBP (in Patients with HT)	89.03 ± 6.39	84.06 ± 7.37	82.61 ± 7.36	81.90 ± 8.74	98.10 ± 7.56	88.40 ± 6.68	88.50 ± 8.75	85.50 ± 7.28
DBP (in patients without HT)	72.09 ± 5.77	74.25 ± 8.18	73.90 ± 7.98	75.01 ± 9.21	76.60 ± 7.22	76.2 ± 8.34	74.60 ± 6.81	73.60 ± 6.99*
Total Cholesterol	4.14 ± 0.89	-	3.96 ± 0.86	4.06 ± 1.04	4.19 ± 0.90	-	3.97 ± 0.79	3.99 ± 0.84
LDL (mmol/L)	2.20 ± 0.66	-	2.27 ± 0.69	2.07 ± 0.71	2.29 ± 0.74	-	2.14 ± 0.59	2.04 ± 0.65
HDL (mmol/L)	1.22 ± 0.29	-	1.19 ± 0.25	1.21 ± 0.22	1.27 ± 0.25	-	1.27 ± 0.23*	1.24 ± 0.23
Triglyceride (mmol/L)	1.20 ± 0.42	-	1.07 ± 0.41	1.12 ± 0.46	1.22 ± 0.52	-	1.08 ± 0.45	1.14 ± 0.53
WBC(10^3/ L)	7.39 ± 1.69	7.34 ± 1.64	7.32 ± 1.66	7.29 ± 1.61	7.24 ± 1.84	7.29 ± 1.56	7.14 ± 1.73	7.20 ± 1.57
Hb(g/dL)	12.98 ± 1.44	13.18 ± 1.50	12.72 ± 1.54	12.51 ± 1.46	12.77 ± 1.37	12.85 ± 1.43	12.54 ± 1.47	12.18 ± 1.38
Platelet(10^3/ L)	260.57 ± 66.54	261.73 ± 63.84	264.98 ± 58.93	263.34 ± 63.90	265.44 ± 53.38	260.80 ± 55.79	259.17 ± 50.294	258.19 ± 49.26
Serum creatinine (μmol/L)	62.55 ± 15.01	64.14 ± 15.26	70.02 ± 15.67	74.61 ± 16.69	59.85 ± 15.02	61.16 ± 15.19	67.60 ± 16.64	73.45 ± 15.15
eGFR (mL/min/1.73 m^2)	96.12 ± 18.67	95.89 ± 16.273	90.24 ± 18.44	85.09 ± 19.97	95.45 ± 18.45	93.58 ± 20.21	88.76 ± 19.44	83.45 ± 18.01
ALT (U/L)	44.11 ± 18.45	43.06 ± 18.20	40.33 ± 17.15	39.43 ± 20.05	43.78 ± 15.78	41.61 ± 16.46	37.72 ± 15.34	37.62 ± 14.98
AST (U/L)	30.06 ± 9.61	30.11 ± 10.49	28.57 ± 9.37	29.67 ± 10.94	31.48 ± 10.47	30.41 ± 8.61	27.33 ± 7.86	28.69 ± 9.46

Data are presented as mean ± SD or percentage(%) SB*P* = systolic blood pressure; DB*P* = diastolic blood pressure, LDL= low-density lipoprotein, HDL= high-density lipoprotein, ALT= Alanine aminotransferase, AST= Aspartate aminotransferase, WBC= White blood cell, Hb= Haemoglobin, eGFR=Estimated Glomerular filtration rate.
HT=Hypertension, Each data point in the raws of the treatment group was statistically compared with the respective data point in the control group. $^{*}P < 0.05$

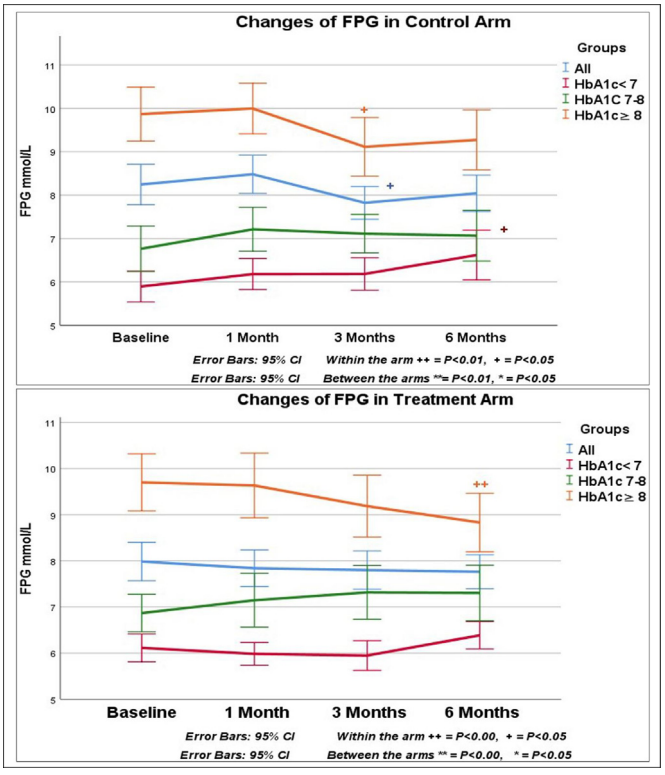

Fig. 4. Changes in the FPG in test and control arms.

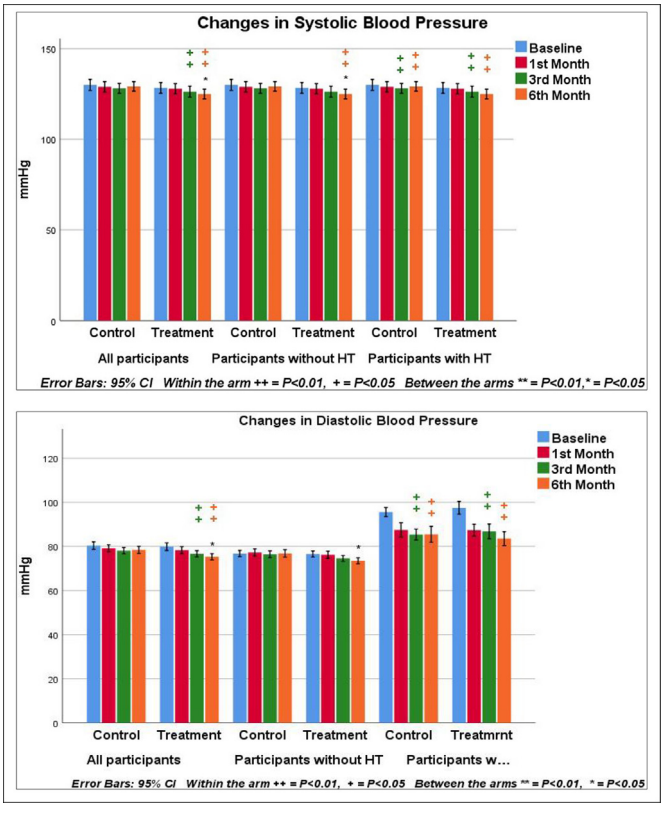

Fig. 5. Changes in the Blood Pressure in treatment and control arms.

Table 4
Adverse effects.

Outcome	Treatment $n = 146$	Control $n = 142$
Adverse Events		
Dizziness	2(1.4 %)	2(1.4 %)
Palpitation	1(<1 %)	0
Tiredness	3(2.1 %)	2(1.4 %)

Even though the diabetic centre patients are on regular clinic follow-up, 52 % of the patients, recruited for this study were observed with poor glycaemic control (HbA1c ≥8). Poor glycemic control T2DM patients are more prone to increased morbidity and mortality due to either the development or progression of diabetic complications. From this study, it came to know that these poorly controlled diabetic patients who were with *G. lactiferum* herbal tea supplementation with proper monitoring arrangement of other parameters, had long-lasting significant reductions in HbA1c. Further to this it controlled elevated blood pressure in hypertension patients, total, LDL Cholesterol and Triglycerides in the third month and over the post-intervention period with no significant reduction in HDL Cholesterol level. Long-lasting control of the above noncommunicable diseases with one cup of Gymnema lactiferum tea per day is very economical to the patients as well as to the health sector. In contrast to the findings of a laboratory study on *G. lactiferum* (Thushari et al., 2010), there was no significant reduction in FPG in this study. As previous studies reported, green tea also showed a significant reduction in HbA1c and a reduction in fasting glucose in the 3rd month (Liu et al., 2013, Park et al., 2014, Nie et al., 2021).

G. lactiferum tea showed a significant long-lasting reduction in systolic and diastolic blood pressure in patients with elevated blood pressure or Patients with hypertension. Green tea also showed a reduction in diastolic blood pressure. Both teas have shown a more significant long-lasting reduction in systolic blood pressure in the participants with hypertension. *G. lactiferum* tea reduced diastolic blood pressure in participants with and without HT (Hypertension), whereas green tea caused a significant reduction in diastolic blood pressure in those with HT. Previous studies reported that green tea significantly reduced SBP(Systolic Blood Pressure) as well (Mousavi et al., 2013, Onakpoya et al., 2014).

The statistically significant, constant reduction in body weight by *G. lactiferum* during the intervention period and post-intervention period suggests that it may be beneficial for weight loss. However, the reduction in body weight was not clinically significant. Unlike previous studies (Basu et al., 2010, Chacko et al., 2010 Zheng et al., 2011, Mousavi et al., 2013, Chen et al., 2016), in the present study, green tea did not cause clinically significant weight loss in the 3rd month, but a statistically significant reduction was elicited in the post-intervention period.

Both teas yielded the same benefits, but due to its widespread use as a home remedy, and ease of cultivation without much expense, G. lactiferum tea is more economically viable as a dietary supplement in controlling diabetes mellitus, hypertension, total cholesterol, LDL cholesterol, Triglycerides, maintain HDL Cholesterol without significant reduction and the reduction of body weight in T2DM patients than Green Tea.

These effects may be more beneficial to those with metabolic syndrome, as it has a beneficial effect on glycaemic control, weight loss and TG. A similar claim has been made for green tea in several studies (Chacko et al., 2010, Kanlaya et al., 2019).

Both *G. lactiferum* tea and green tea were well tolerated. Neither of the preparations caused any hypoglycaemic episodes in the study. The liver enzymes ALT and AST showed a statistically significant reduction lasting over the post-intervention period in the treatment arm. Although there was a reduction in eGFR and Hb, they were within the normal range. In contrast to the present findings, the literature claims that green tea increases eGFR and reduces creatinine levels (Kanlaya et al.,

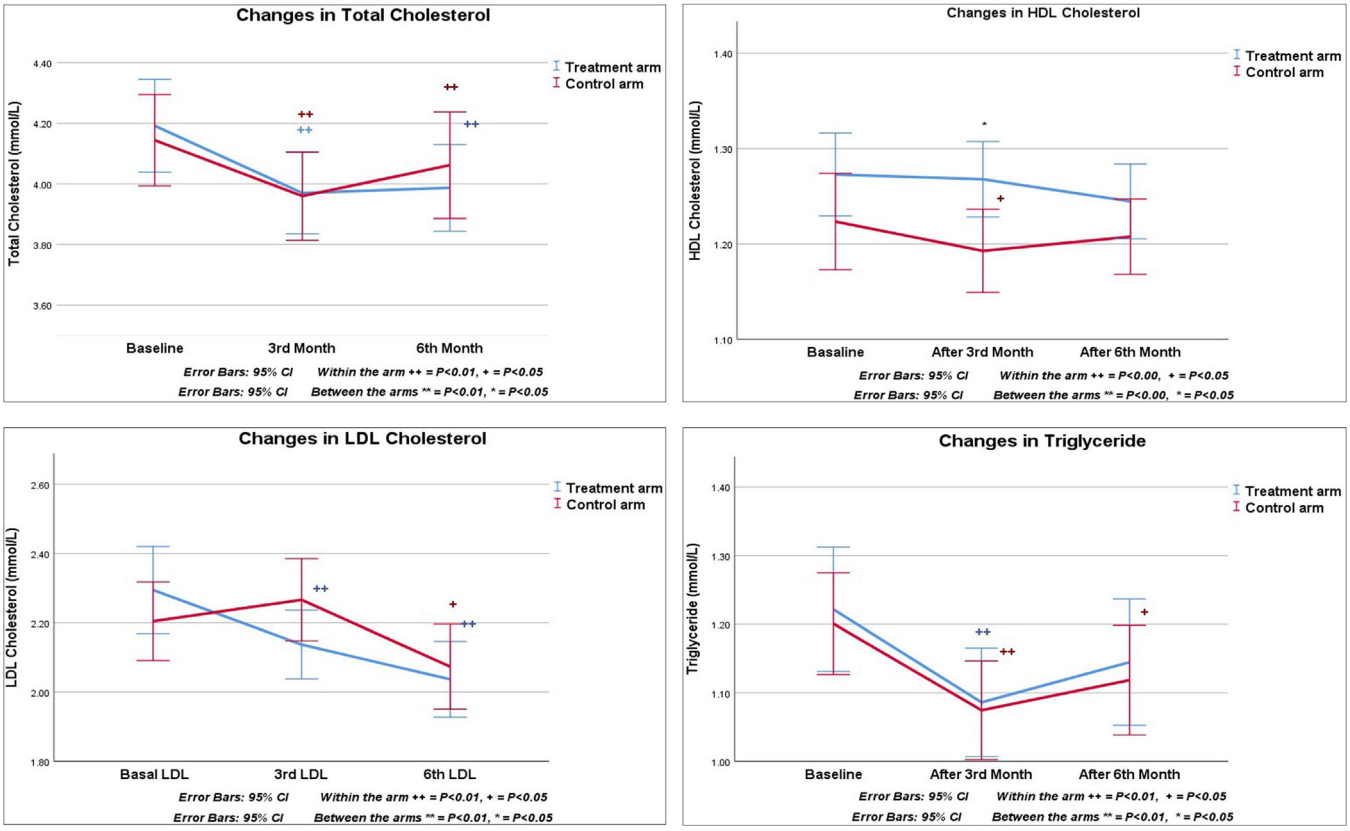

Fig. 6. Changes in the Lipid Profile in treatment and control arms.

2019, Zhang et al., 2022). In one of the recent studies with green tea (600 mL of green tea per day for one month) serum creatinine levels did not significantly change, suggesting renal filtration was unaffected and there was no significant difference in full blood count parameters post-green tea consumption (Essex et al., 2019). As many participants in both arms had multiple comorbidities and were taking multiple medications, we could not say whether these findings were due to intervention or contributed by other factors such as comorbidities and medications. Monitoring HbA1c, FPG, Lipid profile, Full blood count, S.Ceratinine and eGFR every 3 months is an essential part of the clinic follow-up of diabetic management. When introducing this food supplement for long-term use to diabetic patients these regular measures should be followed strictly.

The findings of this short-term RCT showed that *G. lactiferum* tea supplementation significantly improved the long-term glycaemic control in participants with poorly controlled T2DM. It also appeared to have additional beneficial effects on blood pressure, body weight, TC, LDL, and TG while HDL remained normal. The overall beneficial effects of both teas yielded the same benefits, but *G. lactiferum* tea is more economically viable as a dietary supplement due to the above-mentioned reason in the discussion. The use of an active control instead of a placebo, the lack of a long-term treatment arm and the long recruitment time of participants due to the prevailing COVID-19 pandemic were the limitations of this study.

5. Conclusion

G. lactiferum tea supplementation significantly reduced HbA1c in T2DM. This long-lasting control of blood sugar in T2DM patients with reductions in hypertension, total cholesterol, LDL cholesterol, TG and body weight will help to reduce the complications of diabetes. Therefore *G. lactiferum* herbal tea may be an appropriate food supplement for diabetes patients if it is introduced to the market with proper monitoring arrangements in their regular clinic. Uncontrolled T2DM patients have a high chance of frequent admissions to the wards due to the progression of complications. Long-lasting control of these non-communicable diseases greatly reduces this type of frequent admission. Reduction in frequent admission to the wards has a great beneficial effect on the medical sector and economy of the countries. Long-term monitoring is necessary to confirm the safety and health benefits of this food supplement's effects on blood pressure, body weight, glucose level, and lipid profile. Blood tests for ALT, AST, FPG, HbA1c, and S. creatine, as well as measurements of blood pressure and body weight, in three-month intervals, are essential for monitoring and managing T2DM patients receiving conventional drugs to confirm their benefits and assess the effectiveness of food supplement utilization.

Ethical approval

Ethical approval was obtained from the Ethics Review Committee of the Faculty of Medicine, University of Jaffna (Reg. No-J/ERC/15/66/NDR/013-11.01.2016), Sri Lanka Clinical Trial Registry (Reg. No - SLRT/2016/007-09.03.2016) and WHO's International Clinical trial registry platform. Universal registration number U1111-1177-0604. Scientific Acronym of the study is SEGLDM study (Supplement effect of Gymnema lactiferum on Diabetes Mellitus).

Inform consent form signed by every participant during the recruitment process.

Data availability

The datasets used and or analysed during the current study are available from the corresponding author upon reasonable request.

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Declaration of competing interest

Kulanayagam Karthigesu has applied patency to this study.

In Sri Lanka on – 07. 12. 2018 and in World Intellectual Property Organization on 06. 11.2022.

Credit authorship contribution statement

All authors contributed to the drafting of the protocol. KK and SS especially contributed to the overall work of the research. KK conducting the research. Fund holders were SS. Laboratory work was contributed by VK. Statistical analysis and drafting of the paper were especially contributed by KK, STN and RS. Quantification of Gymnemic acid and writing and editing of the paper was done by SP.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ctmp.2024.200164.

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